products in contractors' catalogues have never been prepared in more than gram scale before and have previously used inferior methods unsuitable for further scale-up. Thus, with this background, finding out that a period of maybe 6 months (in worst cases even longer) has to elapse before the eagerly desired starting material is in your storage facility should not come as a surprise! With this in mind, the initiation of external contractors' work covering, for example, the production of a crucial building block should be evaluated and considered without for a moment ignoring the economical risk involved at this early stage before a CD has even been firmly chosen.

A solution to this dilemma that aims to minimize the obstacles already outlined and ensuring the speediest possible supply of materials will inevitably rely on the involvement of Process R&D already in the pre-CD phase. A conceptual model for how this can be arranged has recently been published[1] and hard facts expressed as 'time to first delivery' have in fact corroborated the validity of the procedure described therein. During the 6–12 months prior to nominating a CD, many of the issues around route discovery, process design, scale-up and technology, cost of goods, SHE (Safety–Health–Environment), lead times for raw materials, and patent/intellectual property questions can be addressed and fed back as an effective means of giving a qualitative input to the CD selection process.

The conclusive and clear-cut message from all this can be summarized as: *Drug discovery today needs more involvement from Process R&D*!

Reference

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Too many targets, not enough target validation ▼

'Correlation does not prove causation'. This aphorism, fundamental in selecting targets for drug development, must be re-emphasized given the great excitement generated by the recent publications from Celera Genomics (in *Science*)[1] and the International Human Genome Sequencing Consortium (in *Nature*)[2] describing the draft sequence of the human genome. In a recent issue of *Drug Discovery Today*[3], Philippe Sanseau described what this wealth of data means to the pharmaceutical industry. To date, the resources of the entire industry have generated drugs interacting with only ~500 molecular targets[4]. As Sanseau emphasized, our task now is to find the best drug targets among the thousands of newly identified genes. With fewer than 35,000 genes (discounting splice variants) in the human genome, this task could be slightly less formidable than first predicted (e.g. Incyte Genomics has reported >120,000 human gene transcripts, with 60,000 unique to its database; http://www.incyte.com/sequence/lifeseq/lifeseqgold.shtml).

How can the biological and chemical tractability of these potential targets be assessed? What are the criteria to justify intensive screening, chemistry and development efforts on each new gene product? In the past few years, the industry has been overwhelmed with targets identified using new tools such as gene expression arrays and expressed sequence tag (EST) databases, and this problem has only intensified with the release of the human genome sequence. Increased screening throughput is clearly not the solution, as this only forces the resource bottleneck downstream into lead optimization and development. Rather, a more rational approach is to eliminate poor targets before compound screening begins, through rigorous biological assessment of a gene product's role in disease.

Currently, the pharmaceutical industry has too many targets and not enough target validation. Target validation, crucial to rational drug design, is a concept often discussed but rarely defined. To address this, Sanseau described several 'discovery genomics' approaches to further evaluate targets uncovered in the human genome sequence. Mining of sequence databases, for example, has already added novel members to gene families of proven therapeutic value, such as G protein-coupled receptors (GPCRs)[5].

However, target validation requires more than just demonstrating correlation. A simple association of gene expression with disease (e.g. generated through a gene array) does not validate a role for that target in the disease. Even a human genetics approach to identify targets associated with disease does not necessarily generate chemically tractable molecular targets. Rather, the goal of target validation is to strengthen correlative data (from gene arrays, EST libraries and proteomics) by demonstrating a causal role for the candidate in a disease model. From a

Box 1. Approaches to assessing novel molecular targets

Correlative data	**Causative data**
Genomic sequence mining	Antisense oligonucleotides/ribozymes
Gene expression arrays	Neutralizing antibodies
Serial Analysis of Gene Expression (SAGE)	Knockout/transgenic mice
EST databases	Small-molecule agonists/antagonists
Proteomics	

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research perspective, validation (or invalidation) is achieved by experimentally modulating the function of a putative target in a defined experimental system, then evaluating any effects on the disease-relevant phenotype (Box 1). As an example, antisense technology has become a popular tool for target validation, because the approach promises a high-throughput and a reliable means of inhibiting potential molecular targets in cell and animal models of disease[6].

As Sanseau related, the industry has developed technology to generate correlative genomics data and screen compounds against many classes of molecular targets. However, to develop innovative drugs, we need smarter and faster target validation, not more uHTS of increasing numbers of new targets. For the pharmaceutical industry, success in the clinic should be the ultimate criterion for target validation. The next challenge is therefore to develop robust tools to assess the disease-relevance of thousands of new gene products arising from the genome project, to select those few targets that are worthy of a full development effort.

References

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Education: the chemistry between academia and industry – Reply ▲

Initial letter: Merritt, A. (2001) *Drug Discov. Today* 6, 287

Response from Jeremy Hinks

In a recent letter, Andrew Merritt raised the question of how industry and academia respond to the changing educational needs brought about by the development of new practices within the industry. In particular, he discussed this issue with respect to the rejuvenated interest in solid-phase chemistry and the development of combinatorial techniques, both in terms of the chemistry itself as well as the supporting technology.

Quite fairly, Dr Merritt comments that both communities have a training responsibility in this area: industry has a commitment to its staff in terms of providing opportunities for continuous professional development (CPD) whilst universities serve a student community that requires educationally sound courses that prepare them for employment. There is no question that universities take this issue seriously. However, there are difficulties in providing tuition in all the specialist areas that feature in the chemical industry as a whole. This highlights the need for CPD exercises put on by employers for employees to further support their development of specialist knowledge.

Courses for undergraduates

A chemistry undergraduate's teaching programme consists of two parts: core and specialist knowledge. Core chemistry makes up the courses attended by an entire undergraduate school. Their content excites significant debate amongst lecturers but their primary aim is to lay a firm foundation of chemical knowledge, the absence of which would compromise the learning experience in any concurrent or subsequent specialization. Specialist chemistries are discussed in advanced courses within the undergraduate school, the ultimate specialization being the choice of subject for a postgraduate study. The ideal educational programme is one in which all new topics of study are placed in context by analysis of previously studied course material.

The content of the core chemistry programme is particularly influenced by the knowledge base of incoming freshers. Their standard has changed over the years such that more theory and practical skills have to be covered in the early undergraduate programme. The core programme has also developed to incorporate key skills. The motivation for this has come from both government and industry and its uptake demonstrates higher education's recognition of the need to change in the face of mutable working practices.

The resulting pressures on the timetable mean that there is not enough time to cover as much specialist material as might once have been the case. Nonetheless, taking the University of Southampton (Southampton, UK) as an example, significant developments are recognized and courses are responsive to them. In terms of solid-phase/combinatorial synthesis, we have lectures and practical courses that develop knowledge by building on experiences gained in traditional chemistries. Particular effort is directed at covering the new technologies in 'appropriate context'. For instance, the very simplicity of much of this chemistry is only understood, and its significance appreciated, given a firm knowledge of the underlying science.

Enlightened collaborations of the type supported by the Industrial Consortium to support Combinatorial and Solid Phase Synthesis (ICCSP, see http://www.chemsoc.org/networks/ccn/index) have helped many institutions develop topical

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